Cancer Experience

at

Maple Biological Research Facility

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List of Abbreviations

HSS	Health Studies Service
HSSSB	Health and Safety Support Services Branch (formerly Occupational Health Branch)
HWL	Handwritten List
JHSC	Joint Health and Safety Committee
MGS	Ministry of Government Services (Ontario)
MOL	Ministry of Labour (Ontario)
MNR	Ministry of Natural Resources (Ontario)
MSDS	Material Safety Data Sheet
OHB	Occupational Health Branch
OCTRF	Ontario Cancer Treatment and Research Foundation
PCMR	Standardized Proportional Cancer Mortality Ratio
PMR	Standardized Proportional Mortality Ratio
SIR	Standardized Incidence Ratio
SMR	Standardized Mortality Ratio
TWAEV	Time-weighted Average Exposure Value

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1. Recommendations

Recommendation # 1

A copy of this report should be presented to and discussed with the Maple Joint Health and Safety Committee.

Recommendation # 2

Toxicological assessment of the chemicals in use at the Maple Research Centre should be continued and updated with an emphasis on cancer, particularly kidney cancer.

Recommendation # 3

Continued evaluation and documentation of any hazardous occupational exposures which exist at the Maple Research Centre should be undertaken and remedial action taken where necessary.

Recommendation # 4

Consideration should be given to the performance of a feasibility study regarding follow-up of the present report. This could involve worker self-surveillance, formal follow-up of the mortality and morbidity of Maple workers, generation of a new and larger multi-centered cohort study or consideration of a case-control study.

2. Executive Summary

Maple Fish and Wildlife Centre is a research facility of the Ontario Ministry of Natural Resources.

Subsequent to the concern of the staff over cancer occurrence in past and present employees, the Ontario Ministry of Labour was asked to investigate.

Epidemiological investigations of this apparent cancer cluster was initially seen to be problematic. Regardless, it was felt appropriate to address the workers' concerns in a comprehensive fashion, realizing that any investigation might not indicate whether an abnormal cancer occurrence exists at Maple.

Documentation of Maple chemical inventories indicates several known or suspect human or animal carcinogens. Reliable and accurate documentation of past occupational exposures to these chemicals is not available.

In cooperation with the Ministry of Natural Resources, various personnel records were assembled and examined to determine their utility in an epidemiological study. Available information permitted the generation of two separate worker cohorts. Seven distinct searches for mortality (deaths) were done for these cohorts. Records of

cancer morbidity (cancer cases occurring, not necessarily deaths) were also searched.

A descriptive report of the occurrence of cases of cancer, proportional mortality and standardized mortality and morbidity ratios are presented. These analyses compare the mortality and morbidity experience of the Maple workers with that of the general population of Ontario in an attempt to determine if a difference in mortality or morbidity experience exists.

The results of the descriptive report and mortality and morbidity analyses indicate that from a general perspective, the Maple worker group appears to be healthier than the general population of Ontario. It is inconclusive whether a greater or lesser cancer occurrence exists at Maple compared to the general population of Ontario. With the exception of kidney cancer, the most common and expected types of cancer occurred. In general, a significant excess number of cases of cancer over that expected was not observed. The observation of 2 deaths from a relatively rare cancer (kidney cancer) is of concern but is inconclusive as to whether this is occupationally linked.

The Health and Safety Support Services Branch of the Ministry of Labour was initially involved in an assessment of the Maple facility. This included an assessment of the current

chemical exposures of the Maple employees. It is recommended that the toxicological assessment of the chemicals in use at Maple should be continued and updated with an emphasis on cancer, particularly kidney cancer. Such assessment would insure that proper care is being taken in the workplace. It might also allow for identification of potential kidney carcinogens in man from which hypotheses for further study could be generated either for a future update of this report or for any large scale study which may be contemplated.

Whether employment in the Maple biological research station is associated with a greater risk of developing cancer remains an unanswered question. A concern regarding kidney cancer has been raised. Further investigative work is recommended to clarify these questions. This could range from worker self-surveillance to a large scale cohort or case-control study.

3. Introduction

Maple Fish and Wildlife Research Centre is a research facility of the Ontario Ministry of Natural Resources (MNR). The facility is located in Maple, Ontario at the Southern Research station, a complex which includes buildings involved in biological research and maintenance, storage and administrative buildings.

In October, 1985 the Maple Research Centre's Joint Health and Safety Committee (JHSC) noted the concern of the staff over the number of cancer cases said to have occurred in past and present employees. Since approximately 1970, ten employees were known to have developed cancer and by October 1985, six had died. A concern was raised as to whether these cancers might be occupationally related.

The objective of this report is to address these concerns and to examine the occurrence of cancer in workers currently or previously employed at the Maple Fish and Wildlife Research Centre. Past employment in the main laboratory research building was of particular concern because of the nature of the work performed there and the history of potential occupational exposures.

The epidemiological study of a cluster of cancer cases is usually difficult. It was decided that some examination of the cancer occurrence at the Maple Research Centre was

necessary, fully realizing at the outset that an answer to the question "Does an abnormal cancer rate exist?" might not be forthcoming.

This report will outline the investigations undertaken and the difficulties encountered both in performance of the review and the interpretation of the results. In addition, during the phase of data collection, an extensive review was undertaken of the existing published literature of health-related effects associated with employment in the biological sciences or related occupations. The results of this review are also presented.

4. Background Information

4.1 Preliminary Investigations

After an initial contact by the chairperson of the Maple JHSC with MNR officials, the Ministry of Labour (MOL) was contacted on October 30, 1985 for assistance in investigation of the concerns of the JHSC from an epidemiological perspective.

At this time, the Health Studies Services (HSS) of the MOL became involved to assess the feasibility of performing an epidemiological study. A site visit was conducted by HSS staff in November, 1985 to meet with members of the JHSC and

to obtain familiarity with the site itself and the work performed.

As shown on the attached map (Appendix), the buildings most directly related to fish and wildlife research are buildings #25 and #6, the Fish and Wildlife Research Building and the Fisheries Research Laboratory. Building #25 is a three story structure which contains fish and wildlife research labs. The work involved in these labs often includes general biological/chemical laboratory work, preserving, slide mounting and necropsies. Employee and administrative offices, employee rest and lunch areas, meeting rooms and a library are also located in this building. Building #6 contains numerous holding tanks for fish, a laboratory area where electrophoresis is performed and office space. The research facility opened in 1948 and employs approximately 50 research personnel at any given time. Personnel may be employed on a permanent (classified) basis or on a contractual or casual basis (unclassified). Workers may be part-time at the research facility, spending time at other work locations or in field work. Unclassified workers may also be seasonally employed.

4.2 Occupational Exposures

In addition to the HSS, the Health and Safety Support Services Branch (HSSSB), formerly known as the Occupational Health Branch (OHB) of the Ministry of Labour was initially

involved to evaluate possible occupational etiologies of the cancer cluster and subsequently to assess the current potential exposures of employees to various organic solvents and other chemicals in use at the research facility. This latter process formed the basis for recommendations to ensure a safe workplace presently at the Maple facility. It also assisted in the attempt to obtain a general profile of past chemical exposures.

Approximately 250 chemical exposures to which staff might be exposed were documented in the research facilities. Material Safety data sheets (MSDS) were requested and reviewed by the HSSSB to determine which chemicals in use posed a significant occupational exposure potential, noting that particular attention must be paid to the use of known and/or suspected carcinogens, as well as substances which have relatively low exposure guidelines or have significant acute effects following exposure. Thirty (30) substances were singled out by HSSSB as requiring special attention to minimize exposure. A number of the chemicals were or are used in minute quantities or very infrequently, factors reducing their potential as occupational hazards. HSSSB identified 5 major solvent contaminants for an air sampling survey, namely formaldehyde, methanol, ethyl alcohol, xylene and benzene. After further consideration of work exposures, formaldehyde and methanol were eventually sampled by HSSSB both in the laboratory setting at Maple and in two separate field locations. In all circumstances, methanol was not found

above the analytical limit of detection. In two laboratories and one field setting, formaldehyde was present above the limit of detection but well below the time-weighted average exposure value (TWAEV) for formaldehyde listed in Ontario Regulation 654/86 under the Occupational Health and Safety Act.

Several compounds in current use at the Maple Research Centre were identified as human or animal carcinogens as indicated in the initial review of the chemical inventory by HSSSB. The more common chemicals are formaldehyde, carbon tetrachloride and benzene. Also included in the list of carcinogens are chloroform, benzidine dihydrochloride, creosote, potassium chromate and dichromate, arsenic acid and o-dianisidine dihydrochloride. Antimony trioxide was also included in the chemical inventory. However, it is the production of antimony trioxide and not the chemical itself that is of suspect carcinogenic potential for man. Therefore, it is unlikely that exposure to antimony trioxide represented a potential carcinogenic exposure in this setting.

Given the lengthy latency periods for cancer development, occupational exposures which occurred during the past several decades are of greater relevance to an epidemiological analysis. However, not unexpectedly, adequate documentation of chemical exposures does not exist for the years covered by this report. It is not possible to estimate exposure levels

nor even to reconstruct a reliable inventory of past chemical exposures. This uncertainty weakens any analysis which attempts to relate health outcomes to occupational exposures.

However, it is suspected that past exposures were qualitatively similar to present exposures, particularly respecting exposure to organic solvents and preservatives. Discussions with Maple research and administrative staff have suggested that quantitatively, past exposure levels may have been greater. Poorer ventilation and variable laboratory procedures are factors which may have accounted for this occurrence. It has also been suggested that certain chemicals such as the solvent carbon tetrachloride may have been used more frequently and in considerably greater quantities in the past.

In Conclusion: Reliable and accurate historical documentation of occupational exposures at the Maple research facility are not available. However, it is known that exposures to formaldehyde and organic solvents such as benzene and carbon tetrachloride did occur on a regular basis. These chemicals are notable because of their known or suspect carcinogenic potential in man.

5. Research Design and Methodology

5.1 Preliminary Considerations

After the initial site visit and in cooperation with MNR, various personnel records were assembled and examined to determine their utility in an epidemiological study. Given the absence of a specific hypothesis (ie. no specific cancer of concern was initially identified) and the interest in assessing the health of workers exposed in the past, it was decided to consider a mortality study (study of the causes of death), specifically a standardized proportional mortality ratio (PMR) analysis or if the data base permitted, a standardized mortality ratio (SMR) analysis. As some of the original ten cancer cases of concern remained alive, consideration was also given to a review of morbidity, (study of the types of cancer cases occurring over time) either as a descriptive report of the cancer experience or again if the data permitted, a standardized incidence ratio (SIR) analysis.

On preliminary investigation, less than 300 workers of both sexes were estimated to have worked at the research facility during the period for which reliable worker lists for classified workers could be generated. Approximately 20 deaths were initially known. Statistical power estimations at that time revealed that there was little chance of carrying out an epidemiological mortality study which would

give significant and meaningful results on a statistical basis or that would have a reasonable chance of answering the original question concerning cancer.

Alternatives were then considered. The involved parties agreed that rather than no further investigation being conducted, at least a descriptive review of the mortality and morbidity cancer experience at the Maple research facility would be desirable. This review would permit a verification of the numbers of workers and deaths involved. In addition, the unexpected occurrence of extremely rare cancers or a large percentage of cancer deaths due to one specific type of cancer might indicate the need to consider further investigation. It was understood that the investigation would be unlikely to decide whether an abnormal rate of cancer exists at the Maple facility.

5.2 Cohort Identification

Rather than simply describing the known mortality experience of Maple research workers (a list generated by the JHSC), it was considered necessary to search systematically for any other deaths or cases of cancer which might be identified and included in the descriptive report. Therefore, the initial approach with respect to mortality would be to begin a death search as if one were planning a SMR or PMR analysis. This would permit systematic data collection for the descriptive report and would also permit verification of the initial

impressions respecting limited sample size and meaningful statistical results.

Fifteen personnel record sources were examined. Historically, personnel records have not been designed for the primary purposes of performing epidemiological studies. Although records may be adequate for the purposes for which they were initially designed, difficulties often arise when attempting to use these records for research purposes.

Initially, personnel records were consulted to determine whether they could be used to generate a systematic list of Maple workers, such as retirees, for which the number and types of deaths could be readily determined. The generation of a systematic subgroup of Maple workers such as retirees would have allowed a more easily performed investigation. However, the completeness for epidemiological purposes of available lists of retirees could not be assured. The most complete and reliable list of workers was a taxation listing of all classified employees on the MNR payroll for 1967-1985. Such records were not available for earlier periods. Given the inability to generate a reliable subgroup of Maple workers, the alternative was to generate a complete list of classified Maple workers who ever worked at the Maple facility between 1967-1985.

Many of the MNR workers identified from the taxation files may not have been involved with the Maple research facility

or more specifically, the research buildings of particular concern. Verification of work location would be necessary and could only be done through a laborious process of locating, obtaining, reading and summarizing hard copy personnel files for the study period in question.

Prior to 1967, lists were not available from which a systematically determined subgroup of workers or a complete cohort of Maple research workers could be generated. However, a handwritten list (HWL) listing personnel files for Maple workers for the years 1951-1972 was made available from a former Maple administrative officer. This list was subsequently shown to be incomplete for research purposes and to include unclassified workers as well as workers from other Ontario MNR research stations. However, after verification of work location, this list could be searched for known deaths and the results reported but any attempt at a combined statistical analysis with the 1967-85 cohort would be inappropriate. The circumstances behind the generation of the HWL were unclear and therefore the possibility existed that an ascertainment bias of undetermined nature may have occurred.

By the above methods, a total of 599 names were gathered as potential Maple workers for the given study periods. Files were obtained and examined for 576 (96%) of these names and they were subsequently classified as described below.

5.3 Vital Statistics Ascertainment

The following searches were done to determine vital status:

i) Hard copy personnel files. Deaths might have been recorded on file; workers still employed in government service were known to be living.

ii) Deceased retiree file 1975-1985 and deceased active employee file, 1967-present.

iii) Ontario Cancer Treatment and Research Foundation (OCTRF) mortality and morbidity records. Incident cancer cases were searched from 1964-1984, cancer deaths for 1950-1963 and all deaths from 1964 to March, 1986.

iv) Ontario Registrar General's records. All known Maple research workers found on both the taxation lists and the handwritten list were searched for death in Ontario from the date they were last known to be alive (as determined from the hard copy files) until August 31, 1986.

v) Ministry of Government Services (MGS) retiree records. A list of identified Maple research workers of unknown vital status was submitted for comparison with MGS pension records. This allowed

identification of retirees still receiving a pension who were thus considered to be alive.

vi) Ministry of Transportation and Communications records. Cohort members with activity in their driver's license files (e.g. renewal) after August 31, 1986 were considered to be alive for the study period.

vii) Statistics Canada records. If a member of the Maple cohort was not definitely known to be alive nor to have died after the above record searches, a check of mortality for all Canada was performed through Statistics Canada in Ottawa.

After these 7 separate checks for mortality, any worker with unknown vital status was assumed to be alive as of August 31, 1986. A list of known deaths and causes of deaths was generated by examination of death certificates for all recorded deaths. A list of known incident cancer cases was also generated. Incident cancer cases include not only those cases known to be living but also cases with known dates of cancer diagnosis who may have died at a later date.

Considering the methodology of cohort identification and vital statistics ascertainment, it was appropriate to consider some basic epidemiological analyses, although the

small sample size was known to be a significant factor limiting the meaningfulness of such analyses.

5.4 Mortality Analyses

Two distinct groups of workers were observed, Group A from taxation files and Group B from the HWL. Not included in Groups A and B were workers whose files were unclear but were felt unlikely to ever have worked at Maple (6 files, 3 per Group). Workers were classified by occupation as shown in Table 1. Maintenance personnel were not included as they spent variable and perhaps short periods of time in the research buildings and were not known to have been based in these buildings.

Because there was concern respecting the particular building of employment, the workers were also classified by known building of employment. This was somewhat difficult as the files were usually unclear in this regard and reliance was placed on interviews with administrative officers and other workers at Maple. Because of these difficulties, the workers were classified by their probability of past employment in the main laboratory building, the Fish and Wildlife Research building #25. The classification used is listed in Table 2. In many circumstances, there was a fair degree of certainty among the current staff interviewed regarding the work location of previous employees.

Table 1

Occupational Classification

Code	
1.	Fish and Wildlife research personnel, including those professionals who were employed at Maple in a scientific capacity. - includes scientists and lab technicians/assistants - includes supervisors and/or directors who may have been involved in research programs in their earlier careers and ultimately became supervisors.
2.	Support staff - includes clerks, stenographers, accountants, and librarians.
3.	Foresters - includes those workers employed at Maple in a scientific capacity in forest research.
4.	Draftsmen

A number of workers identified as having worked at Maple were short-term employees. Considering the diagnosis of interest as cancer, a disease generally requiring long-term exposures, a subgroup of workers (A_1) was chosen who were employed 2 or more years at Maple. Observation of workers with lesser terms of exposure would have little relevance to the question of cancer in relation to occupational exposures.

A comparison of observed number of deaths versus expected number of deaths based on rates observed in the Ontario population was undertaken. A computer program written by Coleman et al. (1986) was used to calculate the number of expected deaths for specific causes of death for five year age group and calendar time periods based on mortality observed in the general population of Ontario.

For the proportional mortality analysis, this comparison was done by multiplying the cause-, age-, sex-, and calendar specific known proportional mortality of the Ontario general population by the total number of deaths observed in each Maple group. Summation over 5 year age groups produced the expected number of deaths for a particular cause of death.

Table 2

Building Location Classification

Code	
A	definitely main Research Building
B	probably main Research Building
C	possibly or probably not main Research Building
D	definitely not main Research Building
E	unknown work building location

Main Research Building = Fish and Wildlife Research Building (#25)

The ratio of the observed number of deaths over the expected number of deaths was then calculated and represents the standardized proportional mortality ratio (PMR). If greater than one, this number indicates that a greater number of deaths were observed than would be expected based on the proportional causes of death in the Ontario population. The

significance of an apparently elevated ratio must be closely examined within the context of each study. Restrictions on the study often do not allow definite conclusions to be made regarding ratios greater or less than 1. Also for a PMR analysis, if a deficit of non-cancer deaths occurs in the study group, the proportion of cancer deaths would appear disproportionately high when in reality it was not, rather non-cancer deaths were disproportionately low. In an attempt to account for this possibility, standardized proportional cancer mortality ratios (PCMR) may be calculated. The procedure is similar to that described above for a PMR, except that the expected number of deaths is calculated from the total number of cancer deaths rather than the total number of all deaths.

Another type of mortality analysis involves calculation of the standardized mortality ratio (SMR). In this case, the Ontario general population mortality rates are compared to the mortality rates in the study group of workers. Calculation of the total number of person-years of follow-up was done as per the format set out by Coleman et al. (1986). Person-years were totalled over the period January 1, 1967 or two years after the date of first Maple work start, whichever date was later to either the date of death or to August 31, 1986, the latest date up to which mortality was observed. The counting of person-years began after the prerequisite 2

years of exposure because exposure was considered necessary before the worker became at risk of developing cancer related to their Maple work experience.

Multiplication of the known mortality rates for death due to a specific cause in the Ontario population for 5 year age- and calendar time periods by the respective number of person-years gives the expected number of deaths to be found for each worker group by sex. The ratio of the observed number of deaths over the expected number of deaths is the SMR. The SMR is not based on proportions and therefore is not subject to the same difficulties of interpretation as the PMR. However, it must again be cautioned that an SMR greater than 1 does not always mean an actual greater rate of the particular cause of death being studied. Factors of statistical significance and limitations in the design of a study will influence the interpretation of the results.

Given that both occupational classification and work location were variables of interest, 3 subgroups of Group A_1 were examined individually, creating 4 subgroups in total. Table 3 lists the make-up of the groups A_1 to A_4. All members of these groups were employed at Maple for 2 years or more. Group A_4 represents the smallest group but also the group of particular interest, namely research personnel who were known to have worked in the Fish and Wildlife research building #25.

Table 3

Composition of Subgroups by

Occupation and Work Location

	All Maple Work Locations	Research Building only (Code A or B)
All occupations (Occupation Code 1 to 4)	A_1	A_3
Research Personnel (Occupation Code 1 or 3)	A_2	A_4

Table 4

Number of Workers in Each Group by Sex *

Group	Male	Female	Total
A	154	81	235
A_1	114	51	165
A_2	109	8	117
A_3	75	37	112
A_4	71	3	74
B	32	15	47
B_1	23	10	33

* Subgroups of Group A (A_1-A_4) and Group B (B_1) were employed at Maple for 2 years or more

Table 4 lists by sex the number of workers identified in Group A (source: taxation files 1967-1985) and Group B (source: HWL) and the number of workers in each subgroup.

Calculation of a SMR implies that a comprehensive assessment of person-years was undertaken for all workers during the study period of interest. We were confident that all eligible workers were found for Group A, however such was not the case for Group B (HWL). Therefore a SMR analysis on the HWL was not undertaken as it would not be a reliable calculation. A PMR analysis is usually done when insufficient data can be gathered to consider a SMR study. It is less conclusive than a SMR analysis, does not yield information on total mortality and is only an approximation of a SMR. Therefore, to present a PMR analysis on a group for which a SMR analysis is done would be redundant, lend no additional information and unnecessarily complicate matters. For these reasons, SMR calculations only are presented for subgroups of Groups A. PMR calculations are given for Group B_1 as derived f om the HWL. Because a review of the relative proportion of cancer cases is worthwhile, PCMR results were calculated for the subgroups of both Groups A and B.

Workers with uncertain dates of employment at Maple were encountered. Eighteen workers were excluded from group A_1 when it could not be determined with certainty that a worker

was employed at Maple for greater than 2 years. Of these 18 workers, 13 probably worked greater than 2 years and 5 probably less than 2 years based on a review of their personnel files. Mortality analyses were also done including those 13 workers employed for probably longer than 2 years but, not unexpectedly, the results were similar to those for group A_1 as discussed in Section 6.

5.5 Morbidity Analysis

Incident cancer cases were searched at the OCTRF for 1964-1984. Besides a descriptive report on these cases, an analysis analogous to a SMR, a standardized incidence ratio (SIR), was considered. The small number of incident cases limits the meaningfulness of this analysis. Just as the number of person-years of life is calculated for a SMR, the number of person-years of disease-free life can be calculated for a SIR. The period observed was from January 1, 1967 to December 31, 1984. Age-, sex- and calendar-specific cancer incidence rates for the Ontario general population were used to calculate the expected number of cancer cases which can then be compared to the number observed in our worker group.

6. Results

6.1 Descriptive Report of Cases

6.1.1 Group A

Of the 235 workers in Group A, there were 21 deaths, 15 among males and 6 among females. The causes of death by sex and category of death for Group A are listed in Table 5.

Within Group A, there were 13 incident cases of cancer, 11 among males and 2 among females. Six of these incident cases (4 male, 2 female) were also reported above as deaths. This means that although they were registered at the OCTRF as cases of cancer while living, they subsequently died and were also reported as deaths. The incident cases of cancer by sex and category of cancer for Group A are listed in Table 6.

6.1.2 Group B

Of the 47 workers comprising Group B (HWL), there were 11 deaths, 9 among males and 2 among females. The causes of death by sex and category of death for Group B are listed in Table 7.

Within Group B, there were 4 incident cases of cancer known, 2 among males and 2 among females. One of these incident cases (male) was also reported as a death. The incident

cases of cancer by sex and category of cancer for Group B are listed in Table 8.

6.2 Mortality Analyses

6.2.1 Standardized Proportional Mortality Ratio (PMR)

Table 9 lists the proportional mortality for members of Group B who were employed at Maple for 2 years or more (Group B_1).

The nature of the original concern about cancer made it of particular interest to examine the mortality among research personnel only (occupation codes 1,3) who were employed in the main Research building for 2 years or more. Given that there was already a very small number of workers comprising Groups B and B_1 (47 and 33 respectively), additional smaller sub-groups were not created.

SMR analyses are presented for Group A, therefore PMR calculations are not presented for this group.

Proportional cancer mortality ratios were calculated for Groups A_1 and B_1. Only 2 cancer deaths were observed for Group B_1 and no PCMR results of significance were obtained. Among the 6 cancer deaths of Group A_1, PCMR calculations revealed a significant result only for kidney cancer based on the same 2 previously observed kidney cancer deaths (PCMR = 19.39, $p = 0.008$).

Table 5

Mortality - Group A

Cause of Death	Male	Female	Total
All malignant neoplasms	6	3	9
- malignant neoplasm of digestive organs and peritoneum	2	0	
- colon	(1)	(0)	
- pancreas	(1)	(0)	
- kidney	2	0	
- malignant neoplasm of lung, trachea and bronchus	1	1	
- malignant neoplasm of breast	1	2	
Cardiovascular and Cerebrovascular	4	2	6
Accidental	1	0	1
Respiratory	1	0	1
Other (not categorized above)	3	1	4
Total	15	6	21

Bracketed numbers are included in sub-totals immediately above

Table 6

Incident Cases of Cancer - Group A

Cancer Type	Male	Female	Total
All malignant neoplasms	11	2	13
- malignant neoplasm of digestive organs and peritoneum	3	-	
- colon*	(2)	-	
- pancreas	(1)	-	
- malignant neoplasm of lung, trachea & bronchus *	2	-	
- breast **	-	2	
- kidney **	2	-	
- prostate	2	-	
- thyroid	1	-	
- unknown site	1	-	
Total	11	2	13

* One case also reported as a death in each category

** Also reported as deaths

Bracketed numbers are included in subtotals immediately above

Table 7

Mortality - Group B

Cause of Death	Male	Female	Total
Cardiovascular/ Cerebrovascular	5	1	6
All malignant neoplasms	2	0	2
- malignant neoplasm of digestive organs and peritoneum			
- colon	1	0	
- malignant neoplasm of lymphatic and hema-topoietic tissue			
- lymphoma	1	0	
Accidental	2	0	2
Other (not categorized above)	0	1	1
Total	9	2	11

Table 8

Incident Cases of Cancer - Group B

Cancer Type	Male	Female	Total
All malignant neoplasms	2	2	4
- malignant neoplasm digestive organs and peritoneum	2	-	
- rectum*	(1)	-	
- cecum	(1)	-	
- breast	-	1	
- cervix	-	1	
Total	2	2	4

* Also reported as a death

Bracketed numbers are included in subtotals immediately above

Table 9

Proportional Mortality Ratios for Selected Causes of Death by Sex for Worker Group B_1*

Cause of Death	Observed Deaths	Expected Deaths	Ratio Obs/Exp	95% C.I.	p ** Value
Males					
All diseases	4***	5.21	0.77	0.3 - 1.1	
All malignant neoplasms	2	1.21	1.65	0.2 - 3.9	
Cancer of the digestive organs	1	0.39	2.58	0.07 - 9.9	
- intestine/ rectum	(1)	0.16	6.14	0.2 - 24	
Cancer of the lymphatic/hema-topoietic system	1	0.13	7.83	0.2 - 30	0.2
Diseases of the circulatory system	1	3.01	0.33	0.008 - 1.3	0.2
Accidents/ Poisoning	2	0.79	2.52	0.3 - 5.9	
- motor vehicle	(2)	0.23	8.62	1.1 - 20	0.02
Females					
All diseases	2***	1.91	1.05	0.2 - 1.1	
All malignant neoplasms	0	0.57	0	0 - 3.0	
Diseases of the circulatory system	1	0.97	1.03	0.05 - 1.0	

* Includes workers from the HWL in all occupations (codes 1 to 4) who were employed for 2 years or more at the Maple facility
C.I. = confidence interval (binomial distribution)
p value for a two-tailed test (binomial distribution)

** Omitted p values are greater than 0.2

*** One male non-cancer death (vascular) and one female non-cancer death (connective tissue disease) reported but not analysed

Bracketed numbers are included in subtotals immediately above

The small absolute numbers of cancer deaths observed within each group decrease the meaningfulness of these PCMR calculations.

6.2.2 Standardized Mortality Ratio (SMR)

There were 165 workers in Group A_1, i.e. workers employed at Maple for 2 years or more, including all occupational categories (codes 1 to 4) and all work building locations (codes A to E). Eleven deaths were observed in this group. There were 74 workers in Group A_4, i.e. workers previously employed at Maple for 2 years or more but limited to research personnel (occupational categories 1 and 3) having worked in the main research building (work building codes A or B). Standardized mortality ratios for Group A_1 are reported in Table 10 and for Group A_4 in Table 11. The results of the analyses for Groups A_2 and A_3 are not presented as they do not add any additional information and would unnecessarily complicate the report. They are also not the subgroups of particular interest.

SMRs were also examined after inclusion of the 13 workers who were excluded from Group A_1 on the basis of uncertain length of employment at Maple. These workers were felt to have worked at Maple probably for greater than 2 years. Among these 13 workers were 4 additional deaths, 2 among males from diseases of the cardiovascular and respiratory system and 2 among females, one from disease of the cardiovascular system

and one from cancer of the breast. The inclusion of these additional workers and deaths did not significantly alter the SMR results for the group although for females the ratio for All Cancers and breast cancer changed to 1.10 and 4.53 respectively based on the one additional breast cancer death. Only 5 out of the 13 workers qualify for inclusion in Group A_4, among them one additional circulatory and one additional respiratory death. No additional cancer deaths were contributed resulting in no change in the observed cancer totals in Table 11. Even if these extra workers were to be included in Groups A_1 or A_4, the implications of the results remain unchanged.

6.3 Morbidity Analyses

Standardized Incidence Ratio (SIR)

There were a total of 13 incident cases of cancer observed for Group A. In Group A, 7 incident cases of cancer not reported as cancer deaths were reported in males. Three of these incident cases were reported as non-cancer deaths. In subgroups A_1 and A_4 there were 10 and 9 incident cases of cancer respectively. Only 2 incident cases were observed for females and one for males in Group B that were not reported as deaths.

Standardized incidence ratios for Group A_1 are reported in Table 12 and for Group A_4 in Table 13.

Table 10

Standardized Mortality Ratios for Selected Causes of Death by Sex for Worker Group A_1*

Cause of Death	Observed Deaths	Expected Deaths	Ratio Obs/Exp	95% C.I.	p ** Value
Males					
All causes	11	22.42	0.49	0.2 - 0.9	0.01
All diseases	11***	20.66	0.53	0.3 - 1.0	0.03
All malignant neoplasms	5	5.54	0.90	0.3 - 2.1	
Cancer of the digestive organs	2	1.72	1.16	0.1 - 4.2	
- intestine/rectum	(1)	0.72	1.38	0.01 - 7.8	
- pancreas	(1)	0.31	3.24	0.3 - 18	
Cancer of the respiratory system	1	1.97	0.51	0.05 - 2.8	
Cancer of the kidney	2	0.13	15.27	1.5 - 55	0.02
Diseases of the circulatory system	3	11.12	0.27	0.05 - 0.8	0.01
Diseases of the digestive system	2	1.06	1.89	0.2 - 6.8	
Females					
All causes	2	4.23	0.47	0.05 - 1.7	
All diseases	2	3.94	0.51	0.05 - 1.8	
All malignant neoplasms	1	1.60	0.63	0.06 - 3.5	
Cancer of the breast	1	0.39	2.58	0.3 - 14	

* Includes workers in all occupations (codes 1 to 4) who were employed for 2 years or more at the Maple facility
C.I. = confidence interval (Poisson distribution)
p value for a two-tailed test (Poisson distribution)
** Omitted p values are greater than 0.2
***One male non-cancer death (neurological) reported but not analysed

Bracketed numbers are included in subtotals immediately above

Table 11

Standardized Mortality Ratios for Selected Causes of Death by Sex for Worker Group A_4*

Cause of Death	Observed Deaths	Expected Deaths	Ratio Obs/Exp	95% C.I.	p ** Value
Males					
All causes	8	11.33	0.71	0.3 - 1.4	
All diseases	8	10.30	0.78	0.3 - 1.5	
All malignant neoplasms	5	2.79	1.79	0.6 - 4.2	
Cancer of the digestive organs	2	0.86	2.32	0.02 - 8.4	
- intestine/rectum	(1)	0.36	2.77	0.3 - 16	
- pancreas	(1)	0.16	6.43	0.6 - 35	
Cancer of the respiratory system	1	1.00	1.00	0.1 - 5.6	
Cancer of the kidney	2	0.07	29.36	2.9 - 103	0.004
Diseases of the circulatory system	2	5.50	0.36	0.04 - 1.3	0.2
Diseases of the digestive system	1	0.56	1.79	0.2 - 10	
Females					
All causes	1	0.39	2.57	0.3 - 14	
All diseases	1	0.37	2.70	0.3 - 15	
All malignant neoplasms	1	0.12	8.57	0.8 - 47	0.02
Cancer of the breast	1	0.02	42.84	4.3 - 240	0.05

* Includes research personnel (codes 1, 3) who were employed for 2 years or more in the Research Building #25
C.I. = confidence interval (Poisson distribution)
p value for a two-tailed test (Poisson distribution)

** Omitted p values are greater than 0.2

Bracketed numbers are included in subtotals immediately above

Table 12

Standardized Cancer Incidence Ratios for Selected Cancers by Sex for Worker Group A_1*

Cancer Type	Observed Cancers	Expected Cancers	Ratio Obs/Exp	95% C.I.	p ** Value
Males					
All cancers	9	8.29	1.09	0.5 - 2.1	--
Cancer of colon	2	0.80	2.51	0.3 - 9.0	--
Cancer of pancreas	1	0.28	3.63	0.4 - 20	--
Cancer of lung, trachea and bronchus	2	1.87	1.07	0.1 - 3.9	--
Cancer of prostate	2	0.97	2.05	0.2 - 7.4	--
Cancer of kidney	2	0.19	10.63	1.1 - 38	0.03
Females					
All cancers	1	3.20	0.31	0.03 - 1.8	--
Cancer of breast	1	0.95	1.05	0.1 - 5.9	--

* Includes Group A workers in all occupations (codes 1 to 4) who were employed for 2 years or more at the Maple Facility. (Excludes 2 members of A_1 with incident cancer occurring before Maple work start)

C.I. = confidence interval (Poisson distribution)
p value for a two-tailed test (Poisson distribution)

** Omitted p values are greater than 0.2

Table 13

Standardized Cancer Incidence Ratios for Selected Cancers by Sex for Worker Group A_4*

Cancer Type	Observed Cancers	Expected Cancers	Ratio Obs/Exp	95% C.I.	p ** Value
Males					
All cancers	8	4.19	1.91	0.8 - 3.8	0.1
Cancer of colon	2	0.40	5.06	0.5 - 18	0.1
Cancer of pancreas	1	0.14	7.26	0.7 - 40	--
Cancer of lung, trachea and bronchus	1	0.93	1.07	0.1 - 6.0	--
Cancer of prostate	2	0.45	4.44	0.4 - 16	0.2
Cancer of kidney	2	0.12	16.63	1.7 - 60	0.01
Females					
All cancers	1	0.21	4.84	0.1 - 13	--
Cancer of breast	1	0.05	18.73	0.5 - 54	0.1

* Includes research personnel (codes 1, 3) who were employed for 2 years or more in Research building #25. (Excludes 1 member of A_1 with incident cancer occurring before Maple work start)

C.I. = confidence interval (Poisson distribution)
p value for a two-tailed test (Poisson distribution)

** Omitted p values are greater than 0.2

7. Discussion

7.1 Descriptive Report

7.1.1 Group A

General examination of the types of disease causing death in Group A reveals that the commonest causes of death were from cancer and cardiovascular/cerebrovascular disease. These are also the commonest causes of death for adults in Canada (1985). Although cardiovascular/cerebrovascular causes are generally more common than cancer causes, the situation is changing so that for particular age groups, cancer is competing with cardiovascular/cerebrovascular causes as the commonest cause of death. Also, there was found less cardiovascular/cerebrovascular disease among Group A workers compared to the general population of Ontario. Therefore, although the finding of 3 more cancer deaths than deaths due to cardiovascular/cerebrovascular disease in Group A does not reliably indicate that cancer was a more common cause of death, it would not necessarily be an unexpected finding in our worker group.

Similarly, general examination of the causes of cancer deaths reveal gastrointestinal, kidney, lung and breast cancer deaths. Examination of Canadian age-standardized mortality rates among males reveals lung cancer to be the most common form of cancer death (excluding non-melanoma skin cancer)

followed by gastrointestinal and prostate cancer deaths (Canadian Cancer Statistics 1987). In females, breast cancer, gastrointestinal cancer and lung cancers are the commonest cancers (excluding non-melanoma skin cancer). Therefore, with the exception of the 2 kidney cancer cases, the pattern of cancer occurrence among the Maple cohort of workers parallels that found among the general Canadian population. Noteably, no lymphatic/hematopoietic cancers nor any liver cancers were observed, diseases of particular interest considering the postulated past exposures of the workers (e.g. solvents).

Inspection of the incident cases of cancer reveals that for males, gastrointestinal, lung, kidney and prostate cancer were diagnosed most frequently among the workers. Two cases of breast cancer were diagnosed for females. For Canadian males, lung, gastrointestinal and prostate cancers are most commonly diagnosed on an age-standardized incidence rate basis and for females, breast cancer is the most commonly diagnosed. These comparisons again exclude non-melanoma skin cancers. With the exception of the 2 cases of kidney cancer (the same 2 who subsequently died and were reported above as deaths), there is again noted to be a similar qualitative incidence of cancer among the Maple workers as among the Canadian population.

7.1.2 Group B

Group B is a much smaller group than Group A and generally represents workers employed at Maple earlier than Group A. The mean age for Group A is 54 years and for Group B is 60 years. Among males, the most common causes of death again occur, namely cardiovascular/cerebrovascular and cancer deaths. Two accidental deaths also occurred. For females, only 2 deaths were recorded, one cerebrovascular and one categorized as "other" (non-cancer cause).

Only 2 incident cases of cancer occurred in each sex in Group B, again representing common cancers, gastrointestinal among males and breast and cervical cancer among females.

7.2 Mortality Analyses

7.2.1 General Comments

It must be emphasized that the small number of workers involved in this study and the consequent small number of deaths seriously limits any interpretations of the data. However, it was decided that some attempt to examine the cancer experience at the Maple facility was warranted because of the workers' expressed concerns. In the initial attempts to simply perform a descriptive report, it became obvious that to systematically compile a list of known cancer deaths and living cancer cases, a sound epidemiological approach to

group identification was necessary. Otherwise, the descriptive report would simply be a reiteration and verification of the list of known cancers provided to us from the JHSC with possibly a few additional cancer cases or deaths that might have come to our attention. Without a systematic approach to cancer identification, we might be failing to observe any number of cancer cases or deaths. Such a descriptive report would have very limited value. Having thus decided to systematically identify Maple workers as well as cancer deaths and incident cases found among them, the approach, almost by default, became similar to a large scale epidemiological mortality or morbidity study. It then became a recurring difficulty to decide when to discontinue further investigation or analysis. After having collected the data for a descriptive report, the question was whether further investigative work should be discontinued with reassurance that any attempt at further analysis would have been inappropriate, inconclusive and perhaps misleading. Perhaps so, but with a data base systematically and painstakingly generated, it seemed appropriate to take the additional steps to actually demonstrate the epidemiological and statistical weaknesses associated with mortality or morbidity analyses of such a small sample using data often inaccurate or incomplete. Considering the professional/ scientific background of the target worker group, it was felt that a more detailed scientific report would be appreciated by the workers for whom this study was prepared.

From purely a scientific standpoint, there are both pros and cons to proceeding with further analyses beyond a descriptive report. Cancer clusters can occur randomly just as clusters of the same number may occur together in a random number table. The Maple workers had a suspicion that there was more cancer occurring at their research facility than would normally be expected. In this way perhaps the workers had identified a "random" cancer cluster and any attempt to demonstrate a significant difference between the worker groups and the comparison group (eg. Ontario population), would be therefore initially biased towards finding a difference. Furthermore, considering the lack of sufficient statistical power of the study to detect small but important effects (eg. an increase in certain cancer types) due to small sample size, the finding of no effect may simply represent a "missed" effect and thus may be mistakenly taken as false reassurance.

There are also a number of innate problems with the study such as exposure histories and confounding exposures (e.g. smoking habits, diet, alcohol intake and socio-economic status) which limit its meaningfulness regardless of sample size. In addition to problems of design, problems of interpretation arise with small numbers of observed deaths and fractional (less than one) expected deaths regardless of apparent statistical significance.

Apart from small sample size, during the phase of data accumulation numerous concerns arose which may have affected the results. Reading of hard copy personnel files to determine work location and dates of work was occasionally very difficult because of unclear or incomplete file information. Misclassification of workers as Maple workers may have occurred. Work building location was commonly not recorded and reliance had to be placed on the memory of current Maple workers or on assumptions based on the nature of the work. Workers initially employed as active laboratory researchers may have eventually become managerial-administrative personnel and therefore would have decreased their laboratory exposures. Certain workers could have spent considerable time in a field location or other locations within MNR where their occupational exposures may have differed significantly from those who remained in the laboratories. The amount of part-time or field work could not be taken into account.

Misclassification of causes of death on death certificates is a source of error in studies of mortality. Deaths outside Canada could not be systematically searched and may have been missed. There were 53 members (23%) of Group A and 23 members (49%) of Group B who were classified as unknown vital status. Attempts at vital status ascertainment were extensive. Therefore, the assumption that these workers were alive at the end of the study is reasonable. However,

the potential still exists that some additional deaths may have been missed.

These various limitations were initially considered but it was decided that some type of investigation was desirable. The approach taken evolved as the work proceeded and at all times attempts were made to adhere to sound epidemiological principles.

7.2.2 Specific Comments

With these thoughts in mind, comments will now be offered with respect to the mortality and morbidity analyses presented previously.

For Group B_1, examination of Table 9 reveals a small number of deaths in each category for both observed and expected deaths. This lends a great degree of uncertainty to the ratios derived. For example, observation of just one more or less death in certain categories may double or halve the mortality ratio. This makes interpretation very difficult, if not impossible. Demonstration of the statistical weakness of the results is shown by the often very wide 95% confidence intervals which, with one exception (motor vehicle accidents), always include one. This means that the real value of the observed/expected ratio may equal one, i.e. that no difference exists between the studied population and the comparison Ontario population. Very wide confidence limits

imply that there is little "confidence" that the calculated ratio actually represents the true situation. The published scientific literature often also quotes the "p value", another statistical test of variability with which some readers of this report may be more familiar. Calculation of the p value further demonstrates the statistical weaknesses of the observed data. P values greater than 0.05 are generally taken as indicating lack of statistical significance. No kidney cancers were observed in this group but one cancer of the lymphatic/hematopoietic system was observed.

A PMR study is influenced by certain factors. Deficits of deaths from one cause may increase the apparent proportion of deaths from another cause. The conclusion that one cause of death is in greater proportion may be erroneous; the actual occurrence is that another cause of death (eg. cardiovascular disease) is in deficit. The Maple group was and is largely a white collar group including professionals. It is known that such groups are often healthier than the general population. For the reasons discussed, this occurrence could distort the ratios found in a PMR study.

In order to examine the proportional occurrence of specific cancers relative to the total cancer occurrence, PCMR results were calculated for both Groups A_1 and B_1. Small numbers of deaths again limit any conclusion, although the previously

discussed 2 kidney cancer deaths give an apparently elevated cancer proportion (PCMR) for kidney cancer in Group A_1.

Examination of the SMR values for Groups A_1 and A_4 as shown in Tables 10 and 11 shows some of the same problems of small sample size, small numbers of observed and fractional numbers of deaths.

Based on 11 observed deaths within Group A_1 the Maple workers appear to be healthier than the general Ontario population with a significantly decreased ratio of death from all causes and all diseases. Within these categories, a statistically significant lesser occurrence of diseases of the circulatory system accounts for a large part of this healthier status. Five and one half deaths from cancer were expected in Group A_1, and only 5 observed, indicating that a large number of cancer deaths significantly greater than that expected was not observed. Although 5 observed deaths occurred in Group A_4 compared to approximately 3 expected, one cannot conclude that a significantly greater number of cancer deaths occurred.

The noteable exception is cancer of the kidney where 2 deaths were observed compared to a fractional number of deaths, 0.13 expected. Both cases were among males, one employed in the main research building (#25) for 12 years and the other for 19 years. Both were research scientists although their areas of work were different (Forestry versus Fish and Wildlife)

and therefore their occupational exposures may have differed significantly. However, employment in the same building implies some similarity of occupational environment, particularly regarding past concerns about the adequacy of total building ventilation. Ages at death were 66 and 74 and diagnoses of cancer were made 24 and 32 years after employment in the main research building (#25) had begun and 8 and 12 years after employment in the main research building had ended.

The results regarding kidney cancer are "statistically significant". One must consider the bias discussed above introduced by examining a suspect cancer cluster; a random event may simply have occurred among the Maple worker cohort. From another perspective, a number of categories and sub-categories of death were examined. It is possible that one or more statistically significant results could be observed if a sufficient number of variables is tested. This situation is analogous to the performance of a battery of medical tests on a person. The chances are greater that you will observe a "false positive" result the greater number of tests performed and an apparently abnormal result may occur in a healthy person.

Finally, and perhaps most importantly, the small size of the sample gives a fractional (0.13) number of kidney cancer deaths expected. Only 2 kidney cancer deaths were observed. Observation of even one kidney death which may have occurred

randomly among the worker groups would also give a statistically significant result.

For all these reasons, a conclusion regarding kidney cancer is not possible from this study.

The SMR analysis for Group A_4 reveals that the 2 kidney cancer deaths fell within this group, i.e. scientific personnel employed for greater than 2 years in the main laboratory building. Apparent elevation of the SMR values for certain other cancer deaths is again inconclusive. The occurrence of one case of breast cancer in females exemplifies the fallacy of relying on statistical tests in such circumstances. The SMR for breast cancer in Group A_4 is over 40, ie. 40 times the expected deaths and the result is found to be statistically significant. However, in a general perspective, it is easy to see that the occurrence of one case of a common female cancer is not surprising and that the SMR analysis and associated statistical tests may be misleading if not considered in context.

Considering the incidence of cancer, comments regarding the SIR results are similar to those for the SMR results. Nine (9) incident cases of cancer were observed and 8.3 expected in Group A_1, and 8 incident cases were observed and 4.2 expected in Group A_4, neither result statistically significant (i.e. $p > .05$). This indicates that a large number of cancer cases significantly greater than that

expected was not observed. The calculated SIRs are again based on a small number of cases and have very wide confidence limits and no conclusions may be made respecting specific cancers. Again, the notable exception is kidney cancer with SIRs = 10.6 for A_1 and 16.6 for A_4, both "statistically significant". These 2 incident cases are the same cases found in the SMR analysis and therefore cannot be considered an independent finding but rather reflect an overlap of the data base. No new concerns have been raised by the SIR analyses and a positive association between cancer and Maple employment is neither ruled in nor ruled out.

8. Literature Review

To provide additional scientific and medical background to this issue, the published literature was searched for information on health-related effects associated with employment as a biologist or biological scientist. No epidemiological studies were found specific to this occupational classification. However, information was available respecting related occupations such as chemists, laboratory technicians, medical scientists, and veterinarians which will now be considered.

Early work by Li et al. (1969) found a significantly higher proportion of deaths from the category All Cancers for white male chemists compared to both professional men and elderly white males. A significant increase was found in the

proportion of deaths from malignant lymphoma and cancer of the pancreas relative to deaths from all causes and deaths from All Cancers. The design of the study potentially allowed for several types of bias and the authors themselves decided that their study was inconclusive.

Olin (1978) reported a mortality study among Swedish male chemists who had performed laboratory work for at least a few years after graduation and worked largely with organic compounds. A significantly increased mortality from All Cancers and specifically for lymphatic/hematopoietic and prostatic cancers was found. The latter observation was based on a small number of observations and could certainly be related to the confounding factor of higher socio-economic status in the study group. In an extension of this mortality analysis, Olin and Ahlbom (1980) again found a significantly higher cancer mortality among chemists compared to a group of architects from the same educational institution. A slight, non-significant, excess of All Cancers was found for chemists compared to the general population. More specifically, significant excesses of brain cancer (gliomas) and lymphatic/hematopoietic tumours were found for chemists versus the general population but not compared to the cohort of architects. Olin and Ahlbom (1982) performed a further mortality comparison of the chemists and architects with mining engineers. A significant increase for the relative risk of cancer was found for mining engineers compared to architects. No significant elevations of cancer risk were

observed for the engineers compared to the general population. The authors theorized that exposure to nitrosamides such as methylnitrosourea is of concern respecting the development of brain tumours in chemists but this remains conjectural.

Hoar and Pell (1981) studied the morbidity and mortality of DuPont chemists and reported male chemists to have lower rates of overall mortality and overall cancer morbidity and mortality compared to salaried employees of the same company. A significant elevation of the incidence rate of melanoma, a type of skin cancer, was found for chemists compared to that expected from the American Third National Cancer Survey. A SMR of 1.72 for cancer of the large intestine for chemists relative to the working non-chemist cohort was noted. This implies an excess of this type of cancer in chemists but the results did not quite reach a statistical level of significance. Significant deficits of lung cancer were noted in both mortality and morbidity analyses and a significant deficit of mortality due to arteriosclerotic heart disease was observed. Exposure involved plastic resins and fibers and plastic products, basic chemicals and finishes, petrochemicals, elastomers and low-level radiation. A recent report updated cancer incidence and mortality in the DuPont company but was not exclusive to chemists (O'Berg et al. 1987). Total cancer incidence and mortality was lower than expected among males whereas among females overall cancer incidence was higher than expected but cancer mortality was

lower than expected. The incidence of malignant melanoma was statistically in excess in both sexes. There was an excess of incident intestinal cancer cases among salaried male employees, but mortality from this cancer was not elevated. Breast and cervical cancer incidence was elevated among females but mortality was not. Notably, kidney cancer incidence and mortality were both significantly decreased among DuPont employees.

Alexander et al. (1982) suggested an occupational etiology for a cluster of brain cancer in a diversified petrochemical plant. The report was inconclusive and exposure to at least 10 carcinogens, including vinyl chloride, an experimental brain carcinogen, was noted.

Reeve et al. (1983) performed a cohort mortality study which suggested a slight increase in the risk of death due to brain tumour among chemical plant employees, particularly those hired before 1945. No statistical analysis was applied and the study was not conclusive. A companion case-control study to the Reeve et al. (1983) study was performed by Bond et al. (1983) using the same chemical plant as a source of cases. Cases of primary intracranial neoplasms were compared to 2 matched control groups in an attempt to identify an etiologic agent for brain cancer. No significant associations with workplace exposures were found.

Wright et al. (1983) found a tendency for chemists with melanoma to have worked predominantly with multiple organic chemicals and to have reported more work with solvents, pesticides, plastics, ionizing radiation and benzoyl peroxide. This study was also inconclusive but served to generate hypotheses requiring further examination.

Bond et al. (1985) also studied other causes of mortality among the white male employees of the population studied by Reeve et al. (1983). A significant excess due to All Cancers, Ill-defined Conditions and External Causes of death were found. A significant deficit from All Circulatory Diseases was observed. The excess of deaths from All Cancers included statistically significant excesses for lung and kidney cancer (SMRs 1.70, 3.48 respectively). Magnesium extraction was a major activity in the chemical plant studied although earlier exposures included chlorine, caustic, ethylene, ethylene glycol, ethylene dichloride and dibromide, carbon tetrachloride, styrene and perchloroethylene. As with most other mortality studies, no specific chemical exposure could be implicated retrospectively in cancer development.

Walrath et al. (1985) studied the causes of death among female chemists and reported a five-fold excess of suicide. Elevation of risk of death for All Cancers was found. Considering specific categories, significant elevations of risk were found for breast, ovarian and lymphatic/ hematopoietic cancers although occurrence of the former 2

cancers are consistent with known epidemiological patterns according to socio-economic factors and not specifically with employment as a chemist. Ascertainment of deaths of female chemists was known to have been incomplete in this mortality study.

Maher and Defonso (1986) studied the mortality among white male research chemists. Significantly lower mortality from All Cancers (SMR = 0.55), respiratory cancer, circulatory disease and external causes was noted. There were no significant elevations of mortality due to any specific cancer. Trends noted in the analysis included an apparent non-significant excess in lymphatic/hematopoietic and digestive cancers consistent with other literature.

Related Canadian work by Gallagher et al. (1986) found a significantly elevated PMR in chemical engineers for malignant melanoma. Chemists had a non-significant trend for an increased risk of melanoma but both the results for chemists and chemical engineers were based on small numbers of deaths and suffer from the problems of interpretation usually associated with PMR studies. Gallagher et al. (1986) noted the consistency of their findings with other epidemiological studies.

A recent review (Moss, 1985) of prospective studies of petrochemical workers concluded that an increased risk of brain cancer is suggested in association with petrochemical

exposure, possibly accompanied by an increased risk of melanoma. No evidence of a specific carcinogen was established in these studies. Given that the chemical exposures of biologists or chemists may differ significantly from the exposures in the petrochemical industry, the relevance of these observations in the present situation may be debated. A subsequent recent case-control study (Thomas et al. 1986) found no excess of brain tumours among persons usually employed in the chemical industry or in petroleum refining. The occupational group "natural scientists" was specifically examined. Three cases of brain cancer were classified by occupation as natural scientists on the death certificates. However, the absence of any natural scientists among a randomly chosen control group did not allow a risk calculation to be performed for this group.

Blair and Hayes (1982) examined the mortality patterns among white male US veterinarians over a 30 year period (1947-1977) by examination of 5016 death certificates. Proportions of deaths were significantly elevated for cancers of the lymphatic/hematopoietic system, colon, brain and skin, but significantly lower for cancers of the stomach and lung. The classification of veterinarians involves a number of quite different occupations. The subclassification laboratory veterinarian showed significant excesses for cancer of the colon and lymphatic/hematopoietic cancers only. Radiation exposure was believed related to the lymphatic cancers whereas a known association of higher socio-economic status

with colon cancer was believed to be at least partially responsible for the increased proportional rate of colon cancer. Only one death from kidney cancer was noted for 110 deaths in the subgroup laboratory veterinarians. Overall, no significant excess of kidney cancers was noted but a trend for a greater number of observed kidney cancers than expected was noted (PMR = 1.44, non-significant).

Scientists with work related to biologists are medical anatomists and pathologists. Harrington and Shannon (1975) studied the mortality of British pathologists and medical laboratory technicians. Significant excesses of death due to suicide for both pathologists and laboratory technicians were observed and a significant excess (SMR = 2.42) of death among male pathologists was observed for neoplasms of the lymphatic/hematopoietic system based on an observed 8 cases. Lower total mortality was noted for both groups in comparison to the general population. Actual occupations and exposures were not known and the apparent increased risk of lymphatic cancer in male pathologists was unexplained. Stroup et al. (1985) reported a significantly elevated SMR (SMR = 2.71) for brain cancer in anatomists based on 10 observed cases from an original cohort of 2239 men. Significantly less overall mortality and mortality due to lung cancer was observed in comparison to the US general population. Specific agents associated with the increased risk were not identified but the authors noted that formaldehyde which causes nasal carcinoma in animals is a chemical to which anatomists are

commonly exposed. The study was incompletely reported and cannot be fully assessed but although causality remains undetermined, these observations generate hypotheses for further study.

In a continuation of a previous mortality study (Harrington and Shannon, 1975) of pathologists, Harrington and Oakes (1984) again reported an overall favourable mortality experience for male pathologists in comparison to the general population. This was notable for death due to All Neoplasms, in particular lung cancer and deaths from diseases of the circulatory and respiratory systems. However, a significant excess of death from brain cancer was noted based on 4 observed cases and, consistent with other published work, a significant excess of death from suicide.

In Summary: Epidemiological work directly relevant to biological research workers is scarce. Studies of related occupations such as chemists have shown inconsistent results respecting overall mortality, All Cancer mortality and specific types of cancer occurrence. Results have suggested increased occurrence of brain, lymphatic/hematopoietic, digestive cancers and malignant melanoma. Medical pathologists and anatomists were found to have lower total mortality but increased occurrence of brain cancer and suicide and possibly lymphatic/hematopoietic cancers. Laboratory veterinarians were found to have significant excesses of colon cancer and lymphatic/hematopoietic cancers

possibly related to factors other than occupational chemical exposure. The published literature is non-specific with respect to occupation and types of exposures and inconsistent with respect to findings. The studies have almost exclusively been mortality studies from which causal associations may not be made. However, the studies generate hypotheses for further study and raise concerns regarding possible association of cancer with employment in the chemical, medical, scientific and veterinary professions.

9. Concluding Remarks

This study was performed and a report prepared in response to Maple workers' concerns. The first step is to present the results of this report to the workers and management at Maple. Consideration of any next steps could start at this level.

Recommendation # 1

A copy of this report should be presented to and discussed with the Maple Joint Health and Safety Committee.

From several perspectives the results of this report are reassuring. The Maple worker group appears to be, in general, a healthier population than the general population of Ontario, particularly respecting cardiovascular disease. This deficiency of a specific cause of death would help contribute to elevated rate ratios for All Malignant

Neoplasms in the proportional mortality analysis. In the mortality analyses not subject to this proportional bias, no greater number of cancer deaths were observed than expected for the Maple workers in general (Table 10). Although more cancer deaths were observed than expected for the category All Malignant Neoplasms (5 observed, 2.8 expected) in research personnel employed for greater than 2 years in the main research building, one cannot conclude that a significantly greater number of cancer deaths occurred. No greater number of incident cancer cases were observed than expected for the Maple workers in general. Again, although more incident cancer cases were observed than expected in the subgroup of research personnel employed for greater than 2 years in the main research building, a significant excess of incident cancer cases was not observed for the category All Cancers.

For various reasons discussed in this report, the apparent trends for elevated rate ratios for some cancers may not represent real occurrences. Further reassurance can be taken from the fact that, with the exception of kidney cancer, deaths from various cancer types were observed qualitatively similar to the general Canadian population. This observation argues against an occupational etiology. Also, against an occupational association is the fact that 1 of the 2 observed kidney cancer cases occurred in a forester and the other in a fish and wildlife biologist, both having different job descriptions and therefore differing occupational exposures. The absence of reliable documentation of past

exposures to known renal carcinogens also makes an occupational association more difficult to make. In addition, no liver cancers or leukemia were found in Group A, cancers of concern with solvent exposures. For Group B, no leukemia or liver cancer was found and only one case of lymphoma was noted. Contrary to published work suggesting an association of chemical exposure and brain cancer, no deaths or incident cases of brain cancer were observed.

Observation of 2 deaths from a relatively rare cancer, kidney cancer, deserves further consideration. No current (living) cases of kidney cancer were observed. Although we cannot definitively conclude that a greater amount of kidney cancer (or other cancers for that matter) exists in association with employment at the Maple research facility, observation of 2 similar relatively rare events is of concern. The interpretation of any statistical analysis does not greatly assist us in this circumstance despite its apparent significance particularly in the absence of a specific pre-existing hypothesis for testing. It remains possible that we are observing simply a random occurrence of two cases. Yet it also remains possible that past employment at the Maple Research Centre or in the biological sciences is associated with development of kidney cancer. Unfortunately, this study has not answered that question.

The question of occupational chemical exposures must be further considered. It is worthwhile to review the types of

cancer which have been found in association with the more common potential exposures postulated for the workers in this study. The International Agency for Research on Cancer (IARC,1982) has classified benzene as being causally associated with cancer in humans. Gaseous formaldehyde and carbon tetrachloride are classified as probably carcinogenic to humans. Benzene exposure is associated with the development of leukemia. Carbon tetrachloride has been associated with liver tumours. In addition, as referenced by IARC, one mortality study among laundry and dry-cleaning workers suggested excesses of liver tumours and leukemia and to a lesser extent cervical and respiratory cancers. Formaldehyde has been associated with nasal cancers in experimental animals exposed by inhalation. Evidence rated as inadequate by IARC has associated skin, prostatic and gastrointestinal cancer with exposure of humans to formaldehyde. No respiratory or nasal cancers were noted in the studies referenced.

Preliminary review of the risk factors associated with kidney cancer in man indicates that tobacco smoking can be considered to be a moderately well established risk factor (Schottenfeld and Fraumeni, 1982). Exposure to coke oven emissions, asbestos and coffee drinking have also been implicated. A genetic predisposition is also possible. In animals, kidney cancers have been produced with exposure to aromatic amines, specifically dimethylnitrosamine, benzidine dyes and gasoline. As with many animal studies,

extrapolation of the results directly to man is not possible. Certain aromatic amines are also known human bladder carcinogens. However, aromatic amines are not known to have been used at the Maple Facility.

In association with their workplace assessment, the HSSSB completed a preliminary review of the carcinogenicity of all chemicals currently in use at the main Fish and Wildlife research building and the Fisheries research laboratory. Noteably, benzidine dihydrochloride was listed in the chemical inventory of the Wildlife Research Section but the degree of its use presently or in the past was not noted. The degree of past exposure, if any, to this chemical may be impossible to establish. It was further noted by HSSSB that a number of stains, dyes and other agents were in use at Maple for which adequate information was not then available to determine their hazard to health, including carcinogenicity. It is unlikely that minute quantities of material used infrequently with proper care would act as an occupational carcinogen. Additional material safety data sheets (MSDS) were required to proceed with further assessment of some of these materials. These should now have been obtained. It would now be useful to continue and update the assessment of the chemical inventories with an emphasis on cancer, particularly kidney cancer, and to consider any additional information not previously available.

Recommendation # 2

Toxicological assessment of the chemicals in use at the Maple Research Centre should be continued and updated with an emphasis on cancer, particularly kidney cancer.

Such an assessment would insure that proper care is being taken in the workplace. It might also allow for identification of potential kidney carcinogens in man from which hypotheses for further study could be generated either for a future update of this report or for any large scale study which may be contemplated.

It is often useful to investigate the occupational history of unusual occurrences, including workplace exposures. It is also usually difficult to do this retrospectively. With respect to the 2 kidney cancer cases, confidentiality considerations would preclude further specific inquiries about each individual's past as it would require specific identification of the workers involved. It could also not be useful as such inquiries will not answer the question of whether the 2 observed kidney cancer cases were caused by occupational exposures.

Any attempt to evaluate whether an occupational hazard to potential carcinogens may have existed is made very difficult by the absence of exposure documentation. This introduces a very important point, namely that appropriate exposure

records should be kept for a workplace with potentially hazardous exposures. Consultation with the appropriate occupational health specialist would reveal if monitoring should be undertaken and if so, what to monitor and how frequently. Other health concerns besides cancer would be considered in this monitoring. The availability of exposure documentation for future health-related reviews could be extremely useful and no longer could it be said that adequate documentation of exposures did not exist.

Recommendation # 3

Continued evaluation and documentation of any hazardous occupational exposures which exist at the Maple Research Centre should be undertaken and remedial action taken where necessary.

This activity could be undertaken by the employer with appropriate occupational health consultation and coordinated by the JHSC.

The question of whether employment in the biological sciences is causally associated with the development of kidney cancer remains unanswered.

In the final analysis, this report has acted as a type of pilot study and has served to generate an hypothesis which may be further studied.

Perhaps the most basic approach to further study involves monitoring for any additional kidney cancer deaths or incident cases. It is possible that a surveillance system could be designed and implemented by the JHSC. However, as this study has demonstrated, the analysis and interpretation of such information is problematic. Confidentiality safeguards would have to be maintained at all times and could make the implementation of such a surveillance system very difficult.

Another approach for consideration involves an update of the present study after several years. This would be a more scientific and reliable method and would achieve the cancer surveillance suggested above. Techniques for improvement of study design would have to be considered which would make interpretation of the study more meaningful. The number of person-years of follow-up would increase and the worker cohort would grow by the addition of new members. However, whether this would sufficiently increase sample size to allow a meaningful and statistically powerful study would have to be determined.

The third alternative for follow-up involves generation of a much larger cohort study by attempting to study additional groups with similar occupational circumstances as that found at Maple. This could include biological research personnel or related professions in other research centres across Ontario or even across Canada. Generation of a larger group

would be difficult and identification of an appropriate cohort may be very difficult, if at all possible. Even if such a study could be completed, generalization of any results to the Maple circumstance may be inappropriate, for among other reasons, known peculiarities of exposure (eg. ventilation) at Maple. The cost, time required and responsibility for such a study would have to be determined.

Finally, performance of a more sizable case-control study could be examined.

Regardless, additional investigation will be required before determining whether the apparently elevated occurrence of kidney cancer observed herein is a spurious finding or whether it is associated with employment in the biological sciences.

Recommendation # 4

Consideration should be given to the performance of a feasibility study regarding follow-up of the present report. This could involve worker self-surveillance, formal follow-up of the mortality and morbidity of Maple workers, generation of a new and larger multi-centered cohort study or consideration of a case-control study.

Such a feasibility study could also consider recent and current experimental and epidemiological studies so that

advantage may be taken of current knowledge including study designs and their usefullness in addressing the present issue.

A number of participants could potentially be involved in this feasibility study and in any forthcoming studies. Involvement of workers, labour or management representatives, government and the scientific community is possible.

In Summary: The Maple worker group appears to be healthier than the general population of Ontario. It is not possible to state whether a greater or lesser cancer occurrence exists among this worker group. With the exception of kidney cancer, the more common and expected types of cancers occurred. Continuation of the toxicological assessment specific to Maple chemical exposures is recommended as is the ongoing documentation of hazardous occupational exposures. Further investigative work is recommended to clarify the question whether employment in the occupational sciences is associated with cancer, in particular, kidney cancer.

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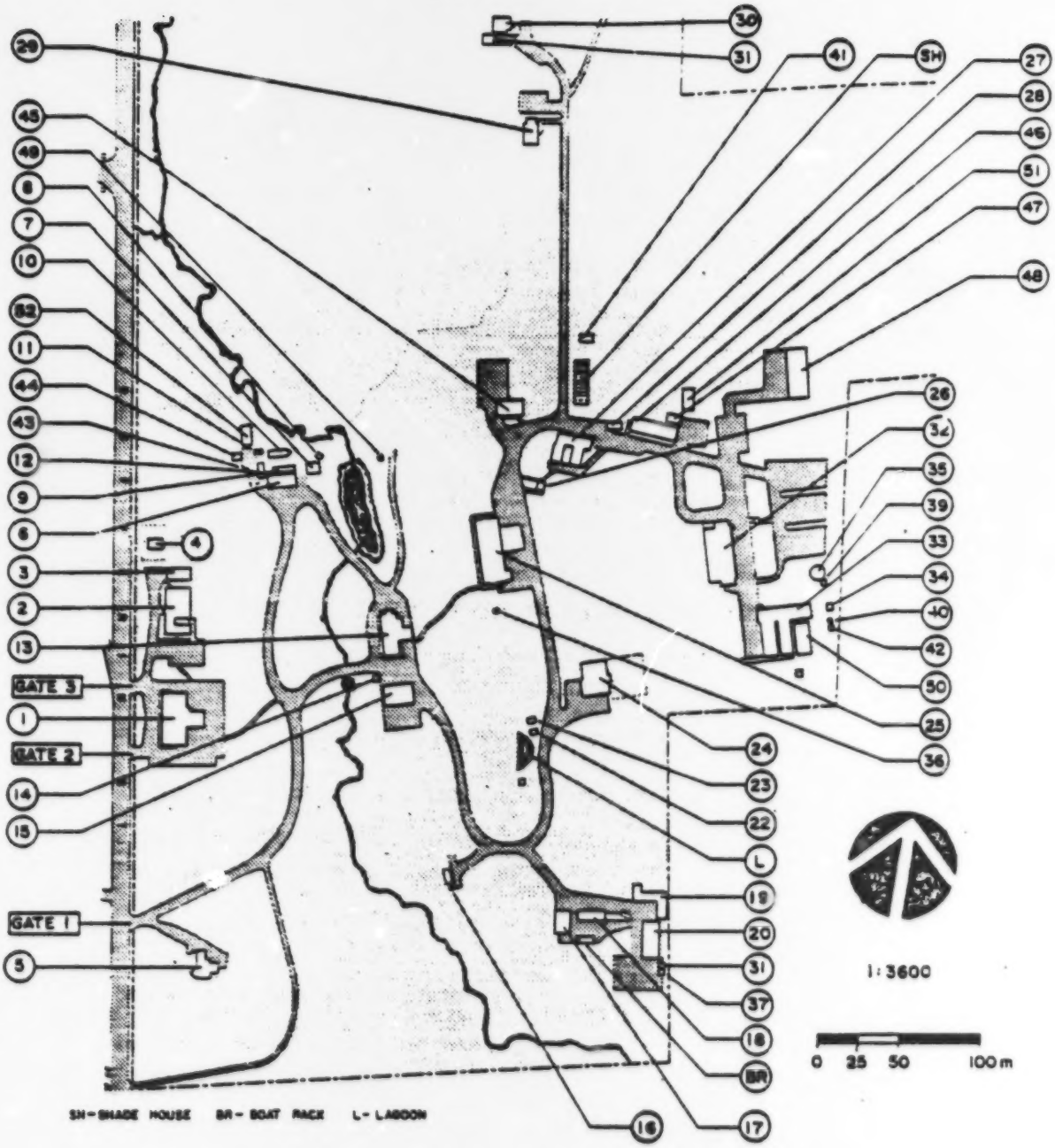
Appendix



S.R.S. NO.	BUILDING NAME	M.G.S. NO.
1	DISTRICT OFFICE & RADIO LAB	12400
2	HUNTER EXAMINATION BLDG.	12401
3	GENERATOR BUILDING	12402
4	QUARANTINE BUILDING	12403
5	PEST CONTROL	12424
6	FISHERIES RESEARCH LAB.	12406
7	PUMPHOUSE NO. 1	15668
8	STORAGE BUILDING	21934
9	CONTROLLED LIGHT BUILDING	12408
10	EARLY REARING FACILITY	12404
11	PUMPHOUSE NO 2	12407
12	STORAGE BUILDING	15689
13	TRILLIUM BUILDING	12408
14	OIL HOUSE	18838
15	STORAGE BUILDING & CARPENTER'S SHOP	12409
16	SEWAGE TREATMENT PLANT	12411
17	STORAGE BUILDING	12423
18	STORAGE BUILDING	12422
19	STORAGE BUILDING	12420
20	QUONSET BUILDING	12421
21	STORAGE BUILDING	18840
22	PUMPHOUSE NO. 4	15671
23	PUMPHOUSE NO. 3	18670
24	WATER TREATMENT PLANT	12412
25	FISHERIES & WILDLIFE RESEARCH	12410
26	STORAGE BUILDING	12413
27	TREE BREEDING BUILDING & GREENHOUSES 1 & 2	12414
28	STORAGE BUILDING	12415
29	RABIES UNIT	12416
30	O.T.I.F. B.I. ANNEX	12417
31	STORAGE BUILDING	15672
32	ONT. TREE IMPROVEMENT & FOREST BIOMASS INST.	12418
33	HEADER HOUSE & GREENHOUSE NO. 5	12419
34	GREENHOUSE NO. 4	18836
35	STORAGE BUILDING	18837
36	WATER TOWER	15674
37	OVERFLOW OFFICE	18834
38	STORAGE BUILDING	18838
39	TRANSMITTER BUILDING	
40	STORAGE BUILDING	
41	MIST HOUSE	
42	STORAGE BUILDING	
43	STORAGE BUILDING	
44	INCINERATOR BUILDING	21848
45	FOREST GENETICS LAB	21847
46	GREENHOUSE NO 5	23964
47	SERVICE BUILDING	23965
48	EQUIPMENT STORAGE	23966
49	PUMPHOUSE NO 5	24489
50	GREENHOUSE NO 6	24611
51	GREENHOUSE NO 7	
52	SALMOND LAB	17596

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